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De Novo Asymmetric Synthesis of Phoracantholide J

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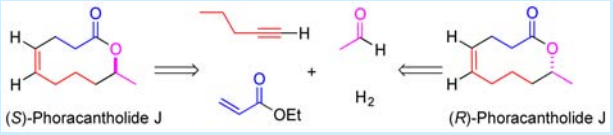
Supporting Information

ABSTRACT: A *de novo* asymmetric total synthesis of the macrolide natural product (*S*)-phoracantholide J has been achieved in 10 steps from the commodity chemicals (1-pentyne, ethyl acrylate, acetaldehyde, and hydrogen). The asymmetry of the route was introduced by a Noyori reduction of a 3-yn-2-one, which makes the route equally amenable to the synthesis of either enantiomer. In addition, this route relies upon an alkyne zipper, a hydroalkynylation, and a macrolactonization to complete the synthesis.



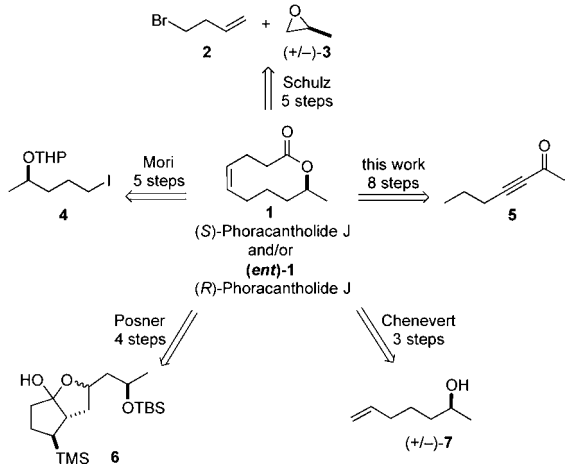
As part of a larger effort aimed at the *de novo* asymmetric synthesis of polyketide macrolactone natural products,[1] we became interested in gaining synthetic access to both enantiomers of phoracantholide J (Figure 1). Both enantiomers of the 10-membered ring macrolide natural product can be found in nature, where they serve as pheromones.[2] In 1976, the *C*-9 (*R*)-enantiomer ((***ent*)-1**) of the volatile phoracantholide J was discovered first as a secretion from the metasternal gland of the Australian beetles, *Phoracantha synonyma*.[3] More recently, the *C*-9 (*S*)-enantiomer of phoracantholide J was isolated from the femoral glands of the Madagascarian frog, *Mantidactylus multiplicatus*.[4] In the beetle, the secretion of (*R*)-phoracantholide J has been shown to serve as a chemical defense mechanism. In contrast, the biological role of (*S*)-phoracantholide J (**1**) has not been verified but due to its association with the frog's femoral gland suggests that it functions as a sex pheromone.

Figure 1. Phoracantholide J (**1**) and enantiomer (***ent*)-1**.

Not long after the discovery of (*R*)-phoracantholide J, it yielded to total synthesis (Scheme 1). The first two racemic syntheses were reported by Petrzilka[5] and later by Malherbe and Bellus[6] using Claisen chemistry. The first asymmetric synthesis was accomplished by Mori in 1983.[7] The synthesis began with (*S*)-3-hydroxybutric acid and occurred through an alkynyl anion alkylation of iodide **4**, followed by Lindlar reduction and macrolactonization.

While the Mori synthesis was lengthy, requiring 20 total steps, it nicely handled the alkene stereochemistry and macrolactone formation. In the years following the first

Scheme 1. Retrosynthesis of Phoracantholide J



synthesis, there were three subsequent syntheses. Chenevert was able to prepare either enantiomer of phoracantholide J using an enzymatic acylation catalyst for the chiral resolution of racemic alcohol (±)-7 along with a ring closing metathesis.[8] To address the issue of alkene stereochemistry, Posner developed an elegant ring fragmentation/macrolactonization approach to (*R*)-phoracantholide J from cyclopentanone via hemiketal **6**.[9] More recently, Schulz developed an enantioselective route to either enantiomer of phoracantholide J from a resolution of racemic propylene oxide ((±)-**3**) and a Wittig olefination to control the alkene stereochemistry.[4] The enantio-divergent biological roles of phoracantholide J piqued our own interest in its *de novo* asymmetric synthesis, as it would allow access to both enantiomers. In particular, we were interested in a synthesis of phoracantholide J that featured the use of the

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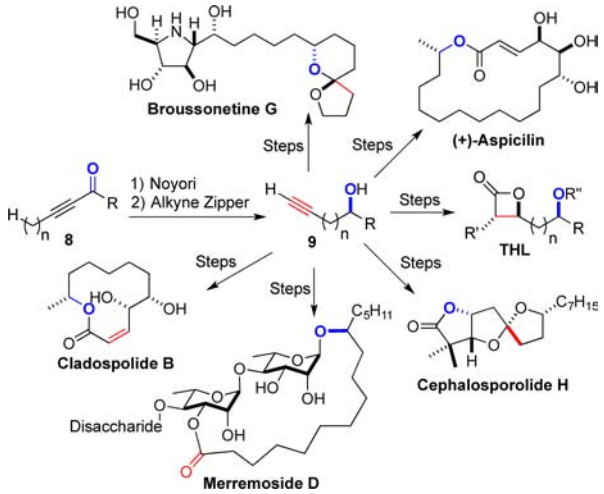
Noyori reduction followed by an alkyne zipper reaction. Herein we describe our successful efforts at the development of a practical *de novo* asymmetric synthesis of either enantiomer of phoracantholide J.

Previously, we[10] and others[11] have shown that the two-step sequence of a Noyori hydrogen transfer asymmetric reduction[12] followed by a KAPA promoted alkyne zipper reaction[13] can be used to convert achiral ynones into ω-yn-ols (**8** to **9**) in good yields and enantiomeric purity (Scheme 2). Examples of the synthetic potential of the approach is outlined in Scheme 2. In an effort to show the synthetic utility of the ω-yn-ol products, we and others have shown that **9** can be transformed into the key component of various natural products, such as the γ-alkoxy spiroketal of broussonetine[11a] and cephalosporolides,[11b] the ω-alkoxy polyol portion of aspicilin,[11c] the alkoxy β-lactone portion of THL,[10b,c] and finally, the ω-alkoxy ester portion of merremoside D[10a] (Scheme 2).

Scheme 2. Use of the Noyori/Alkyne Zipper in Synthesis



Retrosynthetically, we envisioned that phoracantholide J **1** could come from a macrolactonization of hydroxyacid **10**, which in turn could come from a Lindlar catalyzed *cis*-reduction of alkyne **11** (Scheme 3). Of particular interest was whether the 4-ynoate ester **11** could be prepared by a transition metal catalyzed hydroalkynylation of ethyl acrylate with hepta-1-yn-6-ol (**12**). If so, we believed that ynol **12** could be prepared from conjugated ynone **5** by a Noyori/zipper reaction sequence, which in turn can be prepared from 1-pentyne (**13**) and acetaldehyde.

Scheme 3. Retrosynthesis of (*S*)-Phoracantholide J

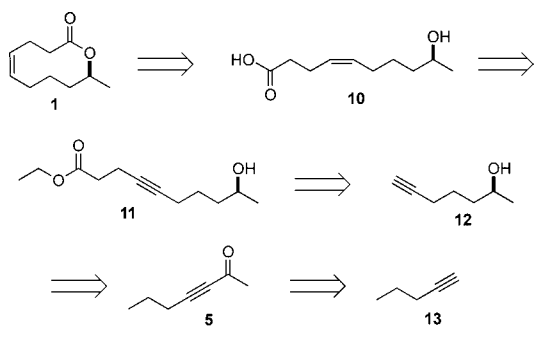
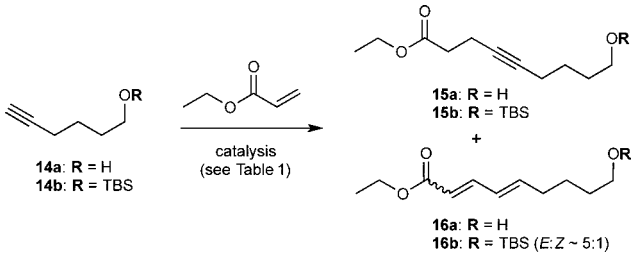


Table 1. Hydroalkynylation of Ethyl Acrylate



entry[a]	alkyne/catalyst/ligand	L/C ratio (mol %)	**15**/**16**[b]	yield[c] (%)
1	**14a**/$Ru_3(CO)_{12}$/[PPN]Cl	10:2	1:1	48
2	**14a**/$Ru_3(CO)_{12}$/[PPN]Cl	2:2	1:2	20
3	**14a**/$Pd_2(dba)_3{\cdot}CHCl_3$/$(o\text{-tol})_3P$	4:4	3:2	25
4	**14a**/$Pd(OAc)_2/Cy_3P$	4:4	NA	trace
5	**14b**/**$Ru_3(CO)_{12}$/[PPN]Cl**	**10:2**	**2:1**	**75**
6	**14b**/$Ru_3(CO)_{12}$/[PPN]Cl	2:2	1:1	39
7	**14b**/$Pd(OAc)_2/(t\text{-Bu})_3P$	4:4	5:4	33
8	**14b**/$Pd(OAc)_2/(o\text{-tol})_3P$	4:4	1:1	20
9	**14b**/$Pd(OAc)_2/Cy_3P$	4:4	1:1	28
10	**14b**/$Pd_2(dba)_3{\cdot}CHCl_3$/$(o\text{-tol})_3P$	4:4	1:1	32
11	**14b**/$Pd_2(dba)_3{\cdot}CHCl_3$/$(t\text{-Bu})_3P$	4:4	1:1	32
12	**14b**/$Pd_2(dba)_3{\cdot}CHCl_3/PPh_3$	4:4	1:2	18
13	**14b**/$Pd(OAc)_2$/NHC	3:3	NA	0

[a]Entries 1−4 were performed in NMP at 95 °C, entries 5−10 were in THF at 60 °C, and entries 11−13 were in THF at rt. [b]The ratio between the isomers **15b**/(2*E*,4*E*)-**16b** was determined by ^{1}H NMR. [c]Yield was isolated yield of the above isomeric mixture, which was purified by HPLC.

In order to search for the optimal conditions for the hydroalkynylation, we chose to study the achiral des-methyl substrates **14a/b** (Table 1). Because we were concerned with the compatibility of the hydroalkynylation reaction with free alcohols, we set out to prepare both ynol **14a** and its TBS-protected variant **14b**. In our survey of the literature for hydroalkynylation reaction, we found two distinct catalyst systems.[14,15] The first uses a Pd(II)/phosphine system, and the second uses a trimeric Ru(0)carbonyl catalyst with the cationic PPN ligand ($Ph_3P{=}N{=}PPh_3Cl$). Our initial survey of both the Pd and Ru catalyst systems with hexynol **14a** (entries 1−4) suggested the poor compatibility of the reaction to primary alcohols. That is to say, significantly improved yields of addition products (**15b**/**16b**) were observed when we exposed the TBS-protected hexynol **14b** to the same reaction conditions (entries 5−13). Both catalyst systems gave the hydroalkynylation addition products along with the isomerization products, dienoates **16a** and **16b**. The $Ru_3(CO)_{12}$/PPN consistently gave better yields of addition products. By increasing the ligand-to-metal ratio (PPN:Ru) and minimizing the reaction time, the direct addition product **15b** could be maximized (entry 5).

After the success of the model system in Table 1, we turned our attention to the real substrate. The synthesis of TBS-protected ynol **18** began with the lithiation of 1-pentyne (**13**) and the addition of the resulting anion to acetaldehyde to form racemic (±)-**17** (Scheme 4). The absolute stereochemistry of (*S*)-**17** was installed by an oxidation and asymmetric reduction sequence, which involved a MnO_2 propargylic alcohol oxidation

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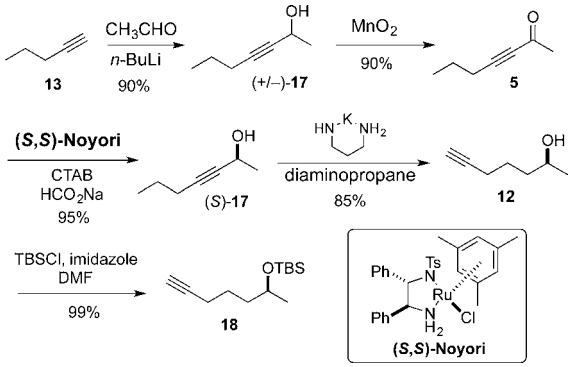
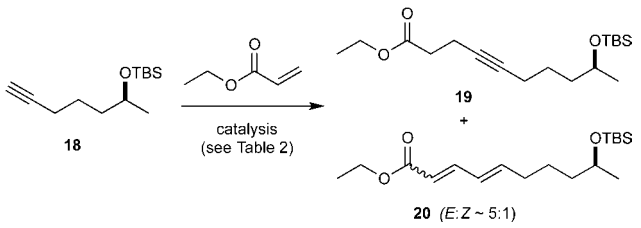
Scheme 4. Noyori/Alkyne Zipper Route to Alkyne 18



and an (*S*,*S*)-Noyori catalyzed reduction with HCO_2Na as the stoichiometric reductant. Exposing enantiomerically enriched (*S*)-**17** to excess KAPA reagent proceeded in excellent yield to give **12** without any erosion of stereochemistry. The protection of **12** as a TBS-ether occurred without incident using TBSCl/imid to give TBS-ether **18**.

With the desired substrate **18** in hand, we next investigated its performance in the hydroalkynylation of ethyl acrylate (Table 2). Subjecting **18** to our previously optimized conditions (entry 1) gave a good yield of addition product **19** with a minimal amount of isomerization. As before, the Pd-catalyst systems gave lower yields of addition product **19** with an increased amount of isomerization product **20**. Similarly, we found that lowering the ligand-to-metal ratio increased the amount of the isomerization of **19** to **20**.

Table 2. Synthesis of 18 via Hydroalkynylation of Ethyl Acrylate

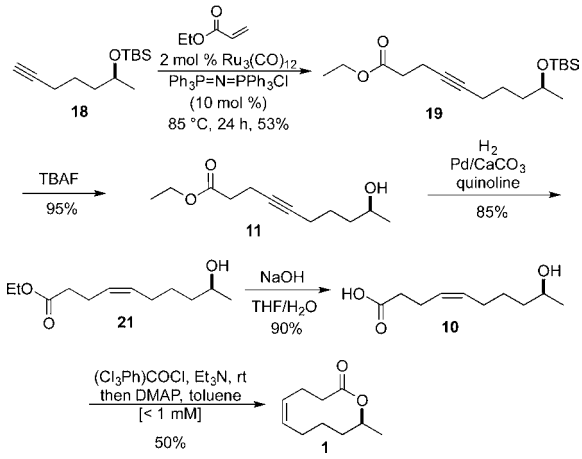


entry[a]	catalyst/ligand	L/C ratio (mol %)	**19**/**20** ratio[b]	yield[c] (%)
1	**$Ru_3(CO)_{12}$/[PPN]Cl**	**10:2**	**3:1**	**70**
2	$Ru_3(CO)_{12}$/[PPN]Cl	6:2	1:1	45
3	$Ru_3(CO)_{12}$/[PPN]Cl	2:2	1:10	40
4	$Pd(OAc)_2$/(*t*-Bu)$_3$P	4:4	1:1	35
5	$Pd(OAc)_2$/(*t*-Bu)$_3$P	4:4	2:1	30
6	$Pd(OAc)_2$/(*o*-tol)$_3$P	4:4	1:1	16
7	$Pd(OAc)_2$/NHC	3:3	NA	0

[a]Entries 1–3 were performed in NMP at 95 °C, entry 4 was in THF at rt, entries 5–6 were in benzene at rt, and entry 7 was in THF at 60 °C. [b]The ratio between the isomers **19**/**20** was determined by ^1H NMR. [c]Yield was isolated yield of the above isomeric mixture, which was purified by HPLC.

With the optimized conditions for the hydroalkyne identified, the reaction was scaled up for the synthesis (Scheme 5). Thus, on a 1 g scale, under these optimized conditions, alkyne **18** reacted with ethyl acrylate to give **19** in a 53% yield. With ample quantities of **19** in hand, the TBS-group was removed with TBAF to give alcohol **11** (95%). The alkyne was reduced

Scheme 5. Synthesis of (*S*)-Phoracantholide J



under Lindlar's conditions to give *cis*-alkene **21** (85%). The required seco-acid **10** was prepared by NaOH promoted ester hydrolysis of **21**. Finally, subjecting **10** to the typical Yamaguchi lactonization conditions provided phoracantholide J (**1**) in a 50% yield.[16] Synthetic **1** thus obtained processed identical spectral data as those reported for the natural material.[4]

In conclusion, a *de novo* asymmetric total synthesis of phoracantholide J was developed from achiral ynone **5** in eight steps and 15% overall yield. As the synthesis uses an asymmetric Noyori hydrogen transfer reaction to install the chiral center in **1**, the synthesis is compatible with the production of either enantiomers of phoracantholide J. In addition to providing access to (*S*)- and (*R*)-phoracantholide J, the synthesis demonstrates the utility of the Ru catalyzed hydroalkynylation reaction in complex molecule synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02432.

Experimental procedures and spectral data for all new compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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